

Structural insights by molecular dynamics simulations on differential repair efficiency for ethano-dA vs. etheno-dA adducts by the human alkyladenine DNA glycosylase (AAG).

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Etheno-dA adducts (ϵ A) are formed by known environmental carcinogens and found to be removed by human alkyladenine glycosylase (AAG). Ethano-dA (EA) adducts differ from ϵ A by change of a double bond to single bond in the 5-member exocyclic ring and are formed by nitrosoureas which can be used in cancer therapy. Here, we show that such a structural change significantly reduces repair efficiency of EA by AAG. The structural reasons for reduced efficiency were studied using molecular modeling. Molecular dynamics (MD) simulation showed similar structural motifs for ϵ A and EA when incorporated into a DNA duplex, suggesting that there are no specific conformational features in the DNA duplex which can account for the differences in the repair efficiency. However, when EA was modeled into the AAG active site, based on AAG/ ϵ A-DNA crystallographic coordinates published by Lau et. al [Lau et. al (2000) PNAS, 97, 13573-13578], in structures produced by 2ns MD, we observed weakening in the stacking interaction between EA and aromatic side-chains of the key amino-acids at the active site. In contrast, the planar ϵ A is better stacked at the enzyme active site. Based on MD, we propose that the observed destabilization of the EA adduct at the active site, particularly reduced stacking interaction, might effect the efficiency of repair. This may provide structural reasons for the biochemically observed weaker recognition of EA by AAG as compared to ϵ A.